REMARKS

Claims 1-4, 7-15 and 35-65 are currently pending in the application. Claims 1, 12 and 55 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Applicant hereby gratefully acknowledge the telephone conference with Examiner Alexander Spiegler on July 2, 2004 wherein Applicant's attorney and Examiner Spiegler discussed the Office Action mailed on April 5, 2004 and the cited prior art.

Priority Claim:

The pending application claims priority to three provisional applications. The Office Action states:

> Applicant's claim to priority of US Provisional Applications 60/213,321, filed on June 22, 2000; 60/234,493, filed on September 22, 2000; and 60/236,649, filed on September 29, 2000, has been acknowledged. However, the instant claims have not been granted priority to any of these provisional applications. Specifically, the instant claims now recite, "a tissue microarray comprising a cooling chamber" (Claim 1), and "a tissue microarrayer comprising a cooling chamber" (Claim 12). The provisional applications do not provide support for the limitations reciting, "a tissue microarray comprising a cooling chamber", and "a tissue microarrayer comprising a cooling chamber". Accordingly, the effective filing date of the instant claims is the filing date of the instant non-provisional application, June 22, 2001. (April 5, 2004 Office Action; Pages 2-3).

In reviewing the above-identified provisional applications, U.S. Provisional Application Serial No. 60/213,321 ("the '321 application") discloses:

> ...In the currently most preferred embodiment the embedding matrix is OCT. **Both the donor and recipient blocks, as well as the donor frozen tissue sample, must be maintained at temperatures at or below -20°C throughout the arraying procedure in order to keep the tissue sample frozen. Additionally, the device that is used to bore tissue samples must be manufactured from a material that can withstand temperatures of –20°C or colder without breaking such as stainless surgical steel with brass fittings.** (the '321 application; Page 8; Lines 2-8)(Emphasis added).

As such, the '321 application discloses the need to maintain the recipient block, the donor block and the frozen tissue in a frozen condition throughout the arraying process. The pending application discloses and claims that a cooling chamber may be used to maintain the recipient block in a frozen condition throughout the arraying process. Therefore, Applicant believes that sufficient support exists in the provisional application to support a device (i.e., a cooling chamber) capable of maintaining the recipient block in a frozen condition throughout the arraying process. Further, the applicant has amended independent claim 1 to read, "...providing a tissue microarrayer comprising a cooling chamber <u>for receiving the recipient block and maintaining the recipient block in a frozen condition</u>..." As such, Applicant believes that the current application is entitled to claim priority to the June 22, 2000 provisional date. Applicant respectfully requests that the Examiner grant priority to the June 22, 2000 date.

<u>Objection To The Specification:</u>

The Office Action objected to the specification of the pending application, stating:

> The disclosure is objected to because on page 22, line 23, the specification recites, "U.S. Patent Application Serial No. 09/779,753", which could be amended to include, "now U.S. Patent No. 6,534,307".
>
> Appropriate correction is required. (April 5, 2004 Office Action, Page 3).

With this Reply, the Applicant has made the requested amendment to the specification. As such, Applicant believes the above-identified objection is obviated.

<u>Rejections Under 35 U.S.C. §112, First Paragraph:</u>

The Office Action rejected claims 1-4 and 7-11 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, stating:

> ...The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.
>
> Claims 1-4 and 7-11 are drawn to a method of "preparing a microarray of frozen tissue...providing a tissue microarray comprising a cooling chamber" (see Claim 1). However, there is no support in the

> specification for a "tissue microarray comprising a cooling chamber". Starting on page 10 of Applicant's response, filed on September 10, 2003, Applicant assert support for the instant claims can be found on pages 22-23, 26 and 28. **These pages refer to a device for generating microarray blocks, referred to as a "microarrayer"**. (See page 22, lines 16-24). Specifically, Applicant incorporates by reference the "microarrayer" which is described in U.S. Patent Application Serial No. 09/779,753 (now U.S. Patent No. 6,534,307). **Accordingly, while there is support for generating a microarray block using a "microarrayer" comprising a cooling chamber, there is no support for a "tissue microarray" comprising a cooling chamber**. (April 5, 2004 Office Action; Pages 3-4)(Emphasis added).

The Office Action states that "there is support for generating a microarray block using "a microarrayer" comprising a cooling chamber. With this Reply, the Applicant has amended all claims to recite **a "microarrayer" comprising a cooling chamber**..." As such, Applicant respectfully requests reconsideration and allowance of claims 1-4 and 7-11.

Rejections Under 35 U.S.C. §112, Second Paragraph:

The Office Action rejected claims 1-4, 7-15 and 35-65 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, stating:

> A) Claims 1-4, 7-11 and 35-65 are indefinite because it is not clear that a "tissue microarray" can comprise a cooling chamber. The specification refers to a cooling chamber that is used in conjunction with a device that forms microarray blocks, but not that the microarray itself comprises a "cooling chamber". (April 5, 2004 Office Action; Page 4)

As stated above, the Applicant has amended all claims to recite **a "microarrayer" comprising a cooling chamber**. As such, Applicant respectfully requests reconsideration and allowance of claims 1-4 and 7-15 and 35-65.

The Office Action continued:

> B) Claims 12-15 are indefinite because it is not clear as to how the "tissue microarrayer" is being used in the method or exactly what is encompassed by the recitation of "tissue microarrayer". For example, step c) is drawn to "providing a tissue microarrayer comprising a cooling

> chamber", however the remainder of the claim makes no mention of the microarrayer or how it is used to create a microarray block. Accordingly, it is not clear as to how step c) is involved with or contributes to the accomplishment of the claimed method. Furthermore, the recitation of "tissue microarrayer" is not specifically defined in the specification. It is noted that the specification refers to a "tissue microarrayer" by incorporation of Applicant's U.S. Patent Application Serial No. 09/779,753 (now U.S. Patent No. 6,534,307); however, this patent does not define this recitation either. More specifically, it is not clear the skilled artisan would know exactly what is encompassed (structurally and functionally) by a tissue microarrayer comprising a cooling chamber, absent any clear structural and functional limitations of the "tissue microarrayer". (April 5, 2004 Office Action; Pages 4-5).

With this Reply, the Applicant has amended independent claim 12 to further define the claimed method. As such, Applicant respectfully requests reconsideration and allowance of pending claims 12-15.

<u>Rejections Under 35 U.S.C. §103(a):</u>

As discussed with Examiner Spiegler, the various cited references disclose a microarrayer capable of preparing microarrays of paraffin (Kallioniemi et al. and Leighton), references which disclose that frozen samples have benefits not found with samples preserved in paraffin (Irving et al. and Goldsworthy et al.) and a reference which show that individual samples may be frozen in a cryostat (Gordon). However, none of the references, alone or in any combination, disclose or suggest a frozen tissue microarrayer comprising a cooling chamber <u>for receiving the recipient block and maintaining the recipient block in a frozen condition</u>. As such, Applicant respectfully requests reconsideration and allowance of pending claims 1-4, 7-15 and 35-65.

More specifically, the Office Action rejected claims 1-4, 7-15 and 35-65 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,103,518 to Leighton in view of Irving et al. (J of Clin. Path. (1996) 49: 258-259), and further in view of U.S. Patent No. 5,533,342 to Gordon. The Office Action stated:

> Leighton teaches a method for constructing tissue microarrays (also referred to as "tissue Chips") comprising,

"taking samples from a series of donor tissues, one at a time, using a hollow, preferably needlelike, donor punch and placing each sample sequentially in a recipient of complementary shape in a recipient material by a recipient punch, thereby forming an array of tissues in the recipient block. Each punch comprises a punch tube and an associated stylet guided within the diameter approximating that of the donor punch inner diameter, and is dimensioned for sliding within the punch tube. **The process of forming a hole in a recipient material such as paraffin, taking a sample of tissue from a donor specimen, and planting this sample in the hole in the recipient material, is repeated until a tissue array is formed comprising hundreds of tissue samples arranged in assigned locations in the recipient material**. (col. 7).

"Once the desired number of tissue samples have been transplanted from the donor block(s) to the recipient block, the "tissue chips" can be formed by slicing the tissue array block into hundreds of consecutive thin sections of, e.g., 5 micrometers in thickness, by traditional means (i.e., microtomes such as Model Cut .sub. 4055.TM. by Olympus Corp. of Tokyo, Japan, etc.; see, e.g., U.S. Pat. Nos. 664,118; 2,292,973; 2,680,992; 3,420,130; 3,440,913; 3,496,819; 3,799,029; and 3,975,977) to create multiple nearly identical sections, with each of the donor cores then being represented as minuscule dots on an ordinary glass microscope slide. Analyses that may be performed on the donor specimens include immunological analysis, nucleic acid hybridization, and clinicopathological characterization of the specimen." (col. 13).

Leighton also teaches:

"The sample punched from the donor tissue sample is preferably cylindrical, about 1-8 mm in length, with a diameter of from about 0.4 to 4.0 mm, preferably about 0.3-2.0 mm. **The recipient punch is slightly smaller than the donor punch and is used to create a hole in a recipient block, typically made of paraffin or other embedding medium**." (col. 7).

Leighton also teaches that the methods can be automated and information for each donor sample in the recipient block is stored in a database (col. 7). Leighton also teaches that this array can be used for many types of samples, including diseased samples (col. 1-4). It is also noted, that with respect to claims 54-65 (claims drawn to contacting the microarray with a molecular probe), Leighton teaches that the array made in his methods can be used in nucleic acid hybridization, which would inherent use a molecular probe for detection (e.g., determining which sublocation react).

Leighton teaches that the tissue samples are embedded in a block of paraffin or other embedding material. <u>Leighton does not specifically teach the use of frozen embedding material</u>.

However, Irving teaches that storing pathological tissue or cell specimens in OCT embedding material (i.e., a frozen embedding material) "permits retrospective analysis of RNA from small amounts of stored pathological samples" (see abstract). In other words, Irving teaches that embedding samples in OCT embedding material produces high quality RNA (i.e., RNA is not likely to get degraded in OCT, as it would in paraffin embedding material) (pg. 258).

Gordon teaches that when tissue samples are stored in freezing embedding material, it is advantageous to perform the preparation of a tissue block in a cooling chamber (e.g., a cryostat or freezing station) (see abstract, and cols. 1, lines 5-12 and 25-62; col. 3, lines 39-67; col. 3, lines 23-67; cols. 5, 7 and 9). Specifically, Gordon teaches,

In a typical prior art procedure for freezing, cutting and preparing a surgical specimen for microscopic examination, the tissue sample is brought into the laboratory for diagnosis while the patient is still on the operating table. Thus, as can be easily appreciated, it is essential to freeze, cut, and diagnose the section of tissue specimen as quickly as possible. Any unnecessary delays can be life threatening. **In order to minimize the time required to perform the critical steps of freezing, cutting and diagnosis of a tissue section, an embedding medium (e.g., an aqueous solution, a viscous aqueous solution, or a viscous aqueous gel) is dispensed onto a specimen holder or block holder which is usually in the form of a small metal block**. The specimen is either placed on top of or submerged into the embedding medium, and then is frozen by any number of means. In most prior art cryostats, the tissue specimen holder is placed on a cold shelf (the freezing shelf) where the medium and tissue specimen are frozen...As can be appreciated, regardless of the freezing technique incorporated, it is generally desirable that the tissue be frozen at the lowest possible temperature (and therefore as quickly as possible) since more rapid freezing results in the formation of smaller ice crystals, and therefore, less damage to the tissue morphology. Also, since the tissue itself is a poor thermal conductor, the best frozen tissue to examine is the tissue at the surface closest to the cooling source. The tissue layers which are further from the surface freeze more slowly (due to the low thermal conductivity of tissue) and therefore have larger ice crystals and poorer quality tissue morphology.

(col. 1, lines 39-62). **Accordingly, Gordon teaches the use of a cooling chamber for preparation of tissue blocks is advantageous for maintaining the integrity of the tissue sample and can minimize the**

> **time required to perform the critical steps of freezing, cutting and diagnosis of a tissue section.**
>
> In view of the teachings of Irving and Gordon, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Leighton so as to have embedded tissue and/or cell samples in OCT embedding material in a cooling chamber, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis). **Furthermore, one skilled in the art would have been motivated to prepare tissue microarrays within a cooling chamber, in order to have maintained the integrity of the tissue sample and minimized the time required to perform the critical steps of freezing, cutting and diagnosis of a tissue section**. (April 5, 2004 Office Action; Pages 5-8)(Emphasis added).

With this Reply, the Applicant has amended independent claims 1 and 12 to recite a method of a producing frozen tissue microarray by using **a tissue microarrayer comprising "a cooling chamber for receiving the recipient block and maintaining the recipient block in a frozen condition; said cooling chamber moveable in an x- and y- direction relative to a fixed horizontal surface."** The amendments are proposed to illustrate that the Applicant has devised a novel device and method which allows for the analysis of frozen tissue samples—an improvement over the analysis of paraffin or other related substances. As such, applicant respectfully requests reconsideration and allowance of claims 1-4, 7-15 and 35-65.

"Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." M.P.E.P. 2143.01. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). See also *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); M.P.E.P. 2143.01.

The Applicant has presented a method of creating a frozen tissue microarray wherein a frozen sample(s) are placed into a frozen recipient block. The cited art does not disclose or suggest a tissue microarrayer which has been adapted to utilize the benefits of maintaining a sample in a frozen state throughout the process and the difficulties that are presented when working with a frozen material as opposed to working with a microarray comprised of paraffin. More specifically, the Applicant's amended claims require a "method for preparing a microarray of frozen tissue and/or cell samples comprising… the steps of: providing a tissue microarrayer comprising a cooling chamber for receiving the recipient block and maintaining the recipient block in a frozen condition; said cooling chamber moveable in an x- and y- direction relative to a fixed horizontal surface;…" As such, the Applicant has provided a novel method of utilizing a microarrayer which has been adapted to overcome the difficulties of processing frozen samples.

As discussed in Applicant's July 11, 2003 Reply to Office Action, support for "a tissue microarrayer comprising a cooling chamber" is found throughout the Applicant's specification. More specifically:

> …As shown in Figure 2, the frozen tissue microarrayer device comprises at least one platform 12 moveable in an x or y direction relative to a fixed horizontal surface 1 and a **cooling chamber 7 for receiving at least one frozen material (e.g., such as a donor block or a recipient block/microarray block) and for maintaining the frozen material in a frozen condition. Preferably, the cooling chamber 7 is moveable with the platform 12, such that when the platform 12 moves in an x-direction, the cooling chamber 12 also moves in an x- direction and when the platform moves in a y-direction, the cooling chamber 7 moves in a y-direction**. (Specification; Page 22, Line 24-Page 23, Line 3)(Emphasis added).
>
> The **cooling chamber** 7 can be cooled in a variety of ways, e.g., by providing the **cooling chamber** 7 with a source of cold water (e.g., water cooled to 1°C to 4°C), a mixture of cold water and ice, or compressed air. In one aspect, the **cooling chamber** 7 comprises sealed tubing configured to form a jacket of cooling fluid (e.g., water or air) around a block of frozen material. An insulator sheet (not shown) also can be placed between the platform 12 and **cooling chamber** 7, to minimize heat dissipation from the **cooling chamber** or heat conduction from the platform 12. In another aspect, the **cooling chamber** 7 further comprises a retaining chamber 6 for retaining at least one block of frozen material.

> The retaining chamber 6 is preferably made of an insulating material for maintaining a temperature of from 0°C to 4°C or below. In some aspects, the retaining chamber 6 is surrounded by cold water, a mixture of ice and water, or cold air (e.g., from a compressed air source which communicates with the cooling chamber 7), or a jacket through which a cooling fluid circulates. (Specification; Page 23, Lines 4-15)(Emphasis added).
>
> In one aspect, the movement of the retaining chamber 6 is coupled to that of the **cooling chamber** 7 which is turn is coupled to movement of at least one platform 12. The movement of the platform 12 can be controlled manually, e.g., by using a grasping element 12g (e.g., such as a joystick) coupled the platform 12, or can be mechanically controlled, e.g., by providing a motor in communication with the platform 12. In one aspect, an x-direction platform 12 in communication with an x-direction motor is provided for controlling movement of the cooling chamber 7 in an x-direction, and a y-direction platform 12 in communication with a y-direction motor is provided for controlling movement of the **cooling chamber** 7 in a y-direction. By providing both platforms, the **cooling chamber** 7 is able to move in both an x- and y- direction. (Specification; Page 26, Lines 10-18)(Emphasis added).
>
> In still a further aspect, a donor block is kept cooled within an insulated **cooling chamber** 7d outside of the device while the recipient block is processed in a **cooling chamber** 7. The **cooling chamber** 7 can then be removed from the device while **cooling chamber** 7d is seated on platform 12 for processing the donor block. (Specification; Page 28, Line 27-Page 29, Line 2)(Emphasis added).

The Office Action held that Leighton in view Irving and further in view of the Gordon reference renders the Applicant's invention obvious. More specifically, the Office Action holds that the Gordon reference provides the motivation to prepare tissue microarrays within a cooling chamber. The Applicant respectfully disagrees that these references, individually or in any combination, render the Applicant's invention obvious.

The Gordon reference discloses a cryostat capable of snap freezing an individual tissue sample and provides a mechanism for cutting accurate and consistent sections of the individual sample for further analysis on a slide. More specifically, Gordon discloses:

> The present invention provides a system and method for **freezing and cutting a tissue specimen** for medical diagnostic purposes which comprises a specimen block holder for holding the tissue specimen; an embedding medium; a freezing plane for providing direct metal contact

> freezing of the specimen; a knife blade comprising a cutting edge which is substantially parallel to and may be displaced a preset distance from the freezing plane; a block holder for holding the specimen; and driving means for transporting the block holder towards the freezing plane for **creating a flat frozen surface of the specimen having a thickness t and also for transporting the frozen specimen past the knife edge to provide a section having a desired thickness**. The planar relationship and known distance between the freezing plane and the cutting edge together will be used as the basis for calculating frozen thickness t of the specimen. **This allows for precise and automated movement of the block holder for trimming**. (Gordon; Abstract)(Emphasis added).

Gordon merely discloses a device capable of snap-freezing an individual tissue specimen. Further, the Gordon reference discloses a device capable of sectioning the individual tissue specimen at a desired thickness for further analysis. However, Gordon does <u>NOT</u> provide the motivation to combine a cooling chamber with a tissue microarrayer <u>wherein the cooling chamber is capable of maintaining the recipient block in a frozen condition during the preparation of the frozen tissue microarray</u>. As illustrative of this fact, Gordon discloses:

> Thermoelectric cooler 44 is thermally coupled to freezing block 42. When a D.C. voltage is applied to electric cables 46, one side of TEC 44 becomes hot and the other side of TEC 44 becomes cold. The hot side is cooled by freezing block 42 and the cold side may be 20° to 40° C. colder. Thus, under steady state conditions, if the "hot" side of freezing block 42 is maintained at –40° C. by mechanical refrigeration means, TEC 44 may generate a "delta T" (i.e., the temperature difference between the hot and cold sides of TEC 44) of between 20° and 40° C. **Under these conditions, the freezing plane 32 will be –60° C. to –80° C.** The D.C. voltage can be reversed at any time, to heat the cold surface and thereby reduce or eliminate frost build-up. (Gordon, Col. 8, Lines 4-16)(Emphasis added).

As such, the Gordon device is designed to snap-freeze a tissue sample to –60°C to –80°C. Alternatively, the cooling chamber of the Applicant's invention is designed to maintain a temperature of approximately 0°C to -20 °C. There is no indication in the Gordon specification that a frozen sample at –80°C can be processed (i.e., cored with a coring needle) the same as a sample at approximately 0°C. As such, there is no indication in the disclosure that the Gordon device could be used as a cooling chamber in combination with the Applicant's claimed invention. Further, the Gordon disclosure never mentions a tissue microarray or a tissue

microarrayer. As such, the Applicant respectfully requests the withdrawal of the above-identified rejections in light of amended independent claims 1 and 12.

The remaining rejections (which substitute the Kallioniemi et al. reference for the Leighton reference and substitute the Goldsworthy et al. reference for the Irving et al. reference) are similar in scope to the above discussed rejection. As such, the analysis and arguments presented above are identical for each rejection. More specifically, none of the references, alone or in any combination, disclose or suggest a tissue microarrayer comprising a cooling chamber for receiving the recipient block and maintaining the recipient block in a frozen condition; said cooling chamber moveable in an x- and y- direction relative to a fixed horizontal surface;..." As such, Applicant respectfully requests reconsideration and allowance of pending claims 1-4, 7-15 and 35-65 as amended.

Double Patenting Rejection:

> The Office Action rejected claims 1-4, 7-15 and 35-65 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 and 19-24 of U.S. Patent No. 6,582,967.

With this Reply, Applicant has filed a terminal disclaimer to facilitate allowance of the pending application.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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